CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The noncancerous lung diseases that have been associated with cigarette smoking in some epidemiologic or population studies are generally grouped together and referred to as chronic obstructive pulmonary disease (COPD). Traditionally, chronic bronchitis and emphysema have been considered to be the main components of this disease group. Any discussion of smoking and COPD is complicated, however, by the often confusing terminology used to refer to this disease entity. These include chronic obstructive lung disease (COLD), chronic obstructive airways disease (COAD), chronic airways (or airflow) obstruction (CAO), and sometimes chronic nonspecific lung disease (CNSLD) or chronic airflow limitation.

As this confusion regarding terminology suggests, scientists have difficulty in understanding the origin and mode of development of these diseases. Certainly, there is much that is unknown about them. Nonetheless, one frequently hears that cigarette smoking is the predominant cause of COPD. However, a critical appraisal of the scientific data suggests that is not a scientifically supportable contention.

Definitions and Terminology

The disease group COPD is manifested by the irreversible inability to blow air rapidly out of the lungs, as if the airways were partially blocked. As noted above, emphysema and chronic bronchitis have historically been categorized as obstructive lung diseases or as components of COPD. Clinicians have used these terms over the years without much regard for the specific definitions set out by experts in pulmonary medicine, but even the experts have disagreed at times about how these diseases should be defined.

For example, there has been and still is much confusion surrounding the definition "chronic bronchitis." The term has had different meanings at different times and in different countries. In the United States, chronic bronchitis has usually been defined by the symptoms of chronic cough and phlegm production, with or without accompanying functional impairment. In Great Britain, on the other hand, chronic bronchitis was used synonymously with COPD. Bronchitis is, in effect, often diagnosed by the patient himself: he is said to have bronchitis if he gives the "right" answers to a set of questions about how much, and how often, he produces sputum. The validity of such a method of diagnosis has been justifiably questioned. To solve these definitional problems, some pulmonary disease experts now recommend that the term "chronic bronchitis" be dropped altogether and that the term "chronic mucus

hypersecretion" be used to indicate a condition leading to chronic cough and phlegm production.

Emphysema, on the other hand, is strictly defined on a pathological basis in a deceased patient. That is, it has a very strict definition that is based on lung changes that can be seen only at autopsy. Therefore, emphysema can be definitively diagnosed only after death. It is characterized by enlargement of the air spaces (alveoli) in the lungs with destruction of the alveolar walls. Because such observations can be made only at autopsy, the diagnosis of emphysema in a living patient is uncertain. However, clinicians often apply this diagnosis to patients who have shortness of breath (dyspnea) and obstructive lung dysfunction.

Attempts to resolve the confusion regarding how to define or measure COPD have encountered difficulties, even among individuals who hold anti-smoking views. For example, an attendee at a meeting of the American Thoracic Society in the early 1960's recalled the "almost endless disagreements" among the participants as they attempted to develop COPD-related definitions.[1] Years later, he observed that "definitions to which everyone will agree are difficult if not impossible to set down."[2] Nor has this definitional confusion been resolved in more recent years. A British professor of thoracic medicine has asserted that typical definitions of chronic bronchitis and emphysema are often used as

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labels which may imply a "well-recognized lung pathology," but for which there is "in fact little or no evidence" in the individual to whom these diagnoses are applied.[3]

The scientific disagreement and confusion regarding the definitions of and the criteria for diagnosing COPD means that it has not been possible to measure accurately the incidence or occurrence of COPD mortality. This, in turn, has serious implications for the validity of the epidemiologic data relating to smoking and COPD mortality.

Epidemiological Studies

The findings of epidemiologic (population) studies are often cited to support the contention that there is a causal relationship between cigarette smoking and COPD. However, as has been frequently emphasized, epidemiologic studies alone do not, and, in fact, cannot establish causal relationships. Although such studies can provide information concerning statistical associations between a factor and a disease, such as cigarette smoking and COPD, such associations do not provide an adequate basis for reaching conclusions about causation. Even the 1964 United States Surgeon General's Report (The Terry Report) conceded:

> Statistical methods cannot establish proof of a causal relationship in an association. The

> causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability.[4]

This scientific principle was reiterated in the 1982 U.S. Surgeon General's Report:

> The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability.[5]

Even though the 1964 report made this concession, the authors of the report set out criteria which, they contended, if met, would allow for reaching a judgment about causation between an agent (such as cigarette smoking) and a disease (such as COPD). Although the criteria have been used in subsequent reports, it has been argued that their usage and the subjective method of "judgment" involved are "inappropriate to a scientific analysis; they should be replaced by the objective testing of hypotheses."[6]

Moreover, even assuming the criteria were valid, an analysis of the data from the epidemiologic studies regarding COPD indicate that they fail to meet those criteria. For example, the authors of the 1964 report argued that to be causal an association had to meet the criterion of specificity. "Specificity" refers to the precision with which the occurrence of the disease (in this case, COPD) can be predicted by the presence of a suspected factor

(in this case, cigarette smoking). The reported epidemiologic association of COPD with COPD mortality does not meet this criterion because cigarette smoking does not predict COPD with high precision; only a small percentage of smokers develop COPD, and COPD also occurs in nonsmokers. In fact, as the 1984 U.S. Surgeon General's Report (the last such report to focus on COPD) conceded, "only 10 to 15 percent of smokers will develop moderate or severe airflow obstruction."[7] Even researchers who believe that cigarette smoking is a risk factor for COPD concede it is "neither necessary nor sufficient" for COPD development because "not all cigarette smokers develop pulmonary obstruction, even at advanced age, and some nonsmokers have COPD at an early age."[8]

Similarly, the reported statistical association of smoking with COPD mortality does not meet the 1964 report's criterion of consistency. This criterion requires that data from epidemiological studies consistently demonstrate an increased mortality from COPD for smokers as compared with nonsmokers. However, the lack of consistency in the data for COPD mortality is evident from variations in the data that cannot be explained by differences in smoking habits. For example, two investigators in the United Kingdom recently noted that although Britain has a higher mortality from chronic bronchitis and emphysema than any other country in Western Europe, "this cannot be explained by international

differences in environmental influences such as cigarette smoking. . . ."[9] Others have reached similar conclusions.[10]

The 1964 report also argued that a causal relationship between smoking and COPD is supported by the temporal nature of the association. This criterion refers to the requirement that exposure to the agent precedes development of the disease. Essentially, this means that changes in tobacco consumption should be followed by parallel changes in COPD mortality after a period of time during which, supposedly, smoking exposure and lung damage accumulate (the latency period). However, a temporal relationship between smoking and COPD mortality has been disputed because emphysema was a well-recognized disease long before cigarette smoking became a popular custom. In 1969, for example, a New York physician who reviewed the medical history of emphysema noted that it had been described almost 300 years ago and that it has been a well-known pathologic and clinical entity since the early 1800's.[11]

Furthermore, claims of a temporal relationship between smoking and COPD are based on the same methodologically weak data as are epidemiological studies concerning smoking and COPD mortality. Perhaps the most notable factor affecting apparent COPD mortality rates may be the changes in how these disease are diagnosed and classified. One well-known antismoking researcher has emphasized that "changing clinical practice and the resulting

changes in the fashion of classifying diseases could account for the trends of COPD mortality that have been reported over the last 30 years."[12] Periodic revisions to the International Classification of Diseases (ICD), which is used to classify causes of death, are assumed to have had dramatic effects on COPD mortality statistics. Perhaps the most significant revision occurred in 1969, when the eighth edition introduced a general code for COPD in addition to the specific codes for asthma, emphysema, and chronic bronchitis. One researcher in the area, despite her strong beliefs concerning a causal role of smoking in COPD, noted that ICD-8's introduction of a COPD code greatly influenced apparent mortality rates:

> COPD was not used as a death certificate code before 1969, but the trend for it and for the combined set of conditions has been upward since then. Thus, a misleading impression is gained, unless the increasing use of COPD is recognized and the combined rate considered. . . .
>
> Knowledge of trends in morbidity and mortality over time is inadequate; the apparent continuing rise in mortality requires more attention and further investigation to determine to what extent the rise is real and to what extent it is due to changing fashions and practices in diagnosis and death certification.[13]

Similarly, a recent report of an analysis of COPD trends in the United States, Canada, and France, concluded that a progressive tendency to code death to a general chronic lung disease

category, stemming from ICD revisions, produced an apparent increase in COPD mortality.[14] The authors of the report, who are antismoking, explained:

> During the 8th revision, there was no category in France for COPD not specified as bronchitis or emphysema, but the U.S. and Canada introduced a special code (519.3), 'chronic obstructive lung disease without mention of asthma, bronchitis or emphysema' (COLD). As more and more U.S. and Canadian death certificates contained nonspecific terminology for COPD instead of bronchitis or emphysema, there was a large increase in the proportion of COPD and asthma deaths classified as COLD, as well as an increase in the total. By 1978, there were more deaths attributed to COLD than to emphysema and bronchitis combined in the U.S.[15]

Earlier ICD revisions may also have had a large effect on reported COPD rates. For example, a medical professor noted that what appeared to be a rise in emphysema rates in the middle of the 20th Century may in fact have been in large part due to ICD coding changes.[16]

There are numerous other weaknesses in the epidemiological data regarding COPD mortality and cigarette smoking. For example, the unreliability of death certificates from which much of this data are derived has been recognized for many years. In fact, as early as 1965, a reviewer with anti-smoking opinions wrote:

> There are a number of studies in the literature comparing the disease listed on the death certificate to the conditions found at autopsy. It is astonishing how poorly these two correlate, particularly in regard to respiratory disease in the United States.[17]

The unreliability of death certificate information has been solidly quantified. In one study from New Zealand, a comparison of death certificate information to necropsy findings revealed over a 50 percent error rate for the diagnosis of respiratory disorders.[18] In fact, overall:

> Errors of epidemiological significance were found in 64.7 percent of the certificates, and in 57.5 percent of individual diagnoses.[19]

The errors appearing in death certificate data arise from several sources, particularly the changes in classification standards and coding practices discussed above, diagnostic unreliability, and a tendency among physicians to give COPD diagnoses more readily to smokers and alternative diagnoses, such as asthma, to nonsmokers. In regard to the latter point, for example, a summary report of the proceedings of an asthma mortality task force in 1987 noted "the apparent diagnostic bias of physicians who are more likely to label women as having asthma than men, and nonsmokers than smokers, and the difficult problem of differentiating asthma from chronic obstructive pulmonary disease in smokers."[20] These sources of error raised serious

questions about the reliability of death certificate data, and the epidemiologic studies which use that data.

Biological Mechanism

The focus of scientific research regarding the pathogenesis, or mechanism, for COPD in humans has primarily been on emphysema. Over the years, various hypotheses have been advanced to explain the mechanism of the development of emphysema. Recently, research efforts have been directed toward the so-called protease-antiprotease imbalance hypothesis. This hypothesis is based on the idea that in the development of emphysema certain proteins normally present in the lung (the proteases and the antiproteases) are thrown out of balance and that, as a consequence, the network around the alveoli and respiratory bronchioli is destroyed. It is also hypothesized that cigarette smoking causes this imbalance to occur.

However, after many years of research, the proposed mechanisms for how emphysema develops and how smoking might cause emphysema remain hypotheses which have not been scientifically established. With respect to the protease-antiprotease hypothesis, for example, the author of a review article, after discussing the uncertainties in the hypothesis, concluded that "despite the research so far, the pathogenesis of emphysema remains obscure."[21] He speculated that even with more research:

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> It is possible that no simple explanation will emerge. Indeed if the pathogenesis was straightforward there would be little current controversy and no flaws in the argument.[22]

Animal Studies

As with studies examining possible biological mechanisms of emphysema, animal studies regarding COPD have focused primarily on emphysema. Although antismokers have sometimes referred to the reported findings of animal studies to support their claims of a causal role for cigarette smoking and emphysema, comments from recent publications indicate that these have failed to demonstrate consistently that smoking causes emphysema. Even the 1984 U.S. Surgeon General's Report conceded that "an animal model for the development of emphysema using the inhalation of cigarette smoke alone has not been convincingly demonstrated."[23] More recently, a 1989 review article stated:

> It has yet to be conclusively shown that there is a laboratory animal model for emphysema produced solely as a result of exposure to cigarette smoke.[24]

The failure of animal studies to reproduce emphysema with cigarette smoke is in marked contrast to those using primary air pollutants,

such as sulphur oxides, which have reportedly led to the production of emphysema in laboratory animals.[25]

This failure has been discussed in light of its broader implications for the scientific understanding of the reported relationship between COPD and smoking:

> Because there is no study that shows that cigarette smoke exposure causes emphysema in a laboratory animal model, the mechanism(s) that might be operative in the development of emphysema from cigarette smoke exposure cannot be predicted. The observations made in the studies designed to elucidate mechanisms cannot be used to support the reported epidemiologic link between emphysema and cigarette smoke in humans.[26]

Other Factors

As with many other smoking-related diseases, COPD is considered to be a multifactorial disease -- a disease in which many factors may be involved in its causation and development. Among the numerous factors which have been associated with emphysema and COPD, in addition to smoking, are occupational exposures,[27] air pollution,[28] repeated acute childhood and adult respiratory illnesses,[29] excessive alcohol consumption,[30] dietary deficiencies,[31] and genetic and familial influences.[32] Researchers have paid particular attention to occupational exposures and air pollution. Pulmonary function abnormalities among workers in such

varying occupations as the coal and the plastic industries, agriculture, and wood processing[33] reflect the diversity of substances which may be involved. Furthermore, reports that air pollution in cities in the United States and France is associated with decreased respiratory function[34] suggest that certain air pollutants may be involved in the causation of COPD and emphysema. The near universality of these factors means that the possible contribution of any one factor to the development of these disease cannot be readily assessed.

Conclusion

COPD is actually a complex and poorly understood set of diseases. The confused clinical picture and lack of agreement regarding the pathogenesis, mode of development, and pathology combine to make this disease virtually undefinable. Yet many discussions treat it as a single, simple entity with only one cause -- cigarette smoking. Until the many areas of confusion are resolved, however, any conclusions about the relationship between COPD and smoking must remain merely conjecture.

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